At this time, Applicants are not aware of any errors in the specification which need to be corrected.

In paragraph 14, on page 3 of the Office Action, the Examiner rejects Claims 9-12 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner states that the term "immunological tolerance" is indefinite.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully submit that the term "immunological tolerance" is well-known and used by those skilled in the art (see the attached PubMed search results for the term "immunological tolerance").

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus request withdrawal of the Examiner's rejection.

In paragraph 16, on page 4 of the Office Action, the Examiner rejects Claims 9-10 under 35 U.S.C. § 102(b) as being anticipated by Ildstad.

Specifically, the Examiner states that Ildstad teaches a method of conditioning a recipient intended for organ grafting by subjecting the recipient to a sublethal total body irradiation and administering to the recipient whole bone marrow, as claimed.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, Applicants note that Claim 11 has not been included in this rejection. Applicants have amended Claim 9 to

include the recitations of Claim 11 therein, thereby canceling Claim 11. Thus, the rejection has been rendered moot.

More specifically, Ildstad relates to a method for conditioning a recipient for bone marrow transplantation by administering to the recipient a dose of total body irradiation from 5.5 Gy to 7.0 Gy, followed by intravenously administering a donor cell preparation containing hematopoietic stem cells which are not compatible with the recipient at the major histocompatiblility complex.

Thus, Ildstad does not teach or suggest "portal venous administration" as recited in amended Claim 9.

Moreover, while the Examiner contends that Ildstad teaches a method involving "administering to the recipient whole bone marrow cells", there is no teaching or suggestion of the same in columns 5, 8, 17 and 21-22 of Ildstad.

Instead, Ildstad describes, at column 7, lines 48 to column 8, line 5, specifically item (2) at column 7, lines 60-62, an approach using "total body irradiation (TBI) followed by the transplantation of a mixture of T-cell **depleted** syngeneic and allogeneic bone marrow cells". In addition, at Section 6.2.1 at column 16, lines 59-61, Ildstad describes that "reconstitution consisted of a mixture of T cell **depleted** (TCD) syngeneic plus TCD allogeneic bone marrow cells".

Thus, Ildstad merely teaches a technique of mixed allogeneic chimerism (see columns 5, 7 and 16, etc., of Ildstad).

On the other hand, the present invention relates to a technique of administering whole bone marrow cells from a graft

donor, which includes T-cells and stromal cells.[1/] More specifically, the present invention relates to a method in which all of the recipient's bone marrow cells are replaced with the allogeneic bone marrow cells from a graft donor. In this respect, the present invention is totally different from Ildstad.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Ildstad, and thus request withdrawal of the Examiner's rejection.

In paragraph 18, on page 5 of the Office Action, the Examiner rejects Claims 9-12 under 35 U.S.C. § 103 as being unpatentable over Ildstad in view of Zhang et al (previously of record).

Specifically, the Examiner states that while Ildstad does not teach hepatic portal vein administration nor transplanting an organ within the same day as administration of the bone marrow, Zhang et al teaches that in both the intravenous and portal vein injections of bone marrow cells, most of the cells migrate to the liver, although more bone marrow cells do so after portal vein administration than after intravenous administration.

Further, the Examiner states that Zhang et al teaches prolongation of organ graft survival in a recipient when cells

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[1/] Ikehara et al, In: New Strategies in Bone Marrow Transplantation, UCLA Symposium on Molecular and Cellular Biology, New Series, Wiley-Liss, Inc., (Champlin RE and Gale PR, eds.); 137:251-257, 253 (1991); a copy of which is attached hereto, teaches that whole bone marrow cells include stromal cells).

from the donor are administrated to the recipient via the portal vein in addition to the transplanted organ.

Hence, the Examiner concludes that it would have been obvious to modify the teachings of Ildstad to administer the donor cells by hepatic portal vein administration to induce immunological tolerance in an organ transplantation recipient, as claimed.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As described above, the present invention differs from Ildstad in that the present invention uses whole bone marrow cells as tolerogen; and the tolerogen is administered through portal venous administration. Because of these distinguishing technical features, the present invention can achieve a successful long-term engraftment of the transplanted organs (see Fig. 2, Group I) which is not predicted from the teachings of Ildstad.

Ildstad does not teach the level of engraftment of transplanted organs (i.e., the rate of transplanted organs successfully engrafted). The description in column 17, lines 4-25 of Ildstad, which the Examiner refers, merely describes the engraftment of transplanted bone marrow cells, but does not teach the engraftment of transplanted organs to which the present invention pertains.

Ildstad does not disclose measurements of the engraftment success rate of transplanted organs.

Furthermore, when the mixed chimerism technique disclosed in Ildstad is used in organ transplantation, the number of transplanted donor allogenic bone marrow cells decreases over

the course of time and soon only the bone marrow cells of the recipient remain. This results in rejection of the transplanted organs (see Hayashi et al, *Stem Cells*, 18:273-280 (2000); and Takao et al, *Immunobiol.*, 194:376-389 (1995); a copy of each of which is attached hereto).

More specifically, Fig. 1 (page 276) in Hayashi et al, *supra*, shows that the numbers of donor cells decrease over the course of time. Further, it is clear from, e.g., the Abstract of Takao et al, *supra*, that the transplanted pancreatic tissues were rejected.

Thus, the skilled artisan would not have been motivated by the teachings of Ildstad to arrive at the distinguished effects achieved by the present invention, i.e., long-term successful engraftment of transplanted organs.

Accordingly, Applicants respectfully submit that Ildstad does not teach or suggest the present invention, and for the following reasons it is clear that Zhang et al does not provide the deficiencies that exist therein.

Zhang et al merely teaches a technique which gives rise to a low engraftment rate of transplanted skin.

Thus, the skilled artisan would not have been motivated or led, by the combination of the teachings of Zhang et al and those of Ildstad, to arrive at successful organ transplantation with long-term engraftment, as achieved by the present invention.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Ildstad alone or when combined with the teachings of Zhang et al, and thus request withdrawal of the Examiner's rejection.

In view of the amendment to the title, claims and Abstract, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

Date: April 29, 2002

A P P E N D I X

Marked-Up Version of Amendments

IN THE TITLE:

The title is amended as follows:

"METHOD FOR INDUCING IMMUNOTOLERANCE [INDUCER] IN AN ORGAN TRANSPLANTATION RECIPIENT"

IN THE CLAIMS:

Claim 11 is being cancelled.

Claim 9 is being amended as follows:

Claim 9. (Amended) A method of inducing immunological tolerance in an organ transplantation recipient which comprises the steps of:

(a) prior to organ transplantation, subjecting the recipient to total body irradiation using a sublethal radiation dose of at least 6.5 Gy, and thereafter,

(b) administering to the recipient a tolerogen effective amount of whole bone marrow cells from a graft donor by hepatic portal venous administration [or by intravenous administration].

IN THE ABSTRACT:

The present Abstract is being replaced by the substitute Abstract attached hereto.